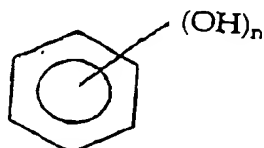


AMENDED CLAIMS

[received by the International Bureau on 06 September 2000 (06.09.00);
original claims 1-32 replaced by new claims 1-35 (6 pages)]

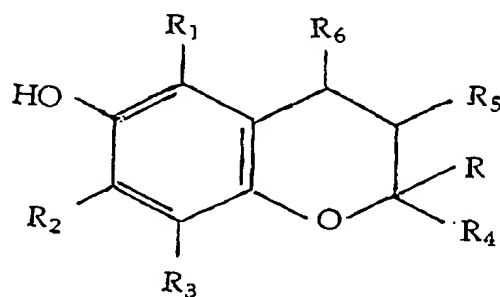
1. A chemical composition having oxygen transporting capability and comprising biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from non-enzymatic phenolic compounds; pyrazolines; carotenoid and retinoid compounds; quinones; tetrapyrroles; indoles and aminoindoles; purine analogs; ascorbic acid; and steroid and alkaloid antioxidants.
2. The chemical composition of claim 1 wherein the antioxidant is a phenolic compound containing one or more groups of formula:



where n is an integer from 1 - 3, the aromatic ring being optionally further substituted, and being optionally fused or linked to another carbocyclic or heterocyclic ring system.

3. The chemical composition of claim 2 wherein the phenolic compound is a polyphenolic, a substituted phenolic, a phenolic ether; a di-tert.butylhydroxyphenylthio-substituted hydroxamic acid; a chroman-based compound such as a chromanol or a dihydrobenzofuranol; a flavanoid or isoflavanoid such as flavanone and dihydroflavanol; a gallate; a catechol or catechol derivative; or a phenolic acid.
4. The chemical composition of claim 3 wherein the phenolic antioxidant is a chromanol.
5. The chemical composition of any preceding claim wherein the oxygen transporting substance is a heme-protein macromolecule.

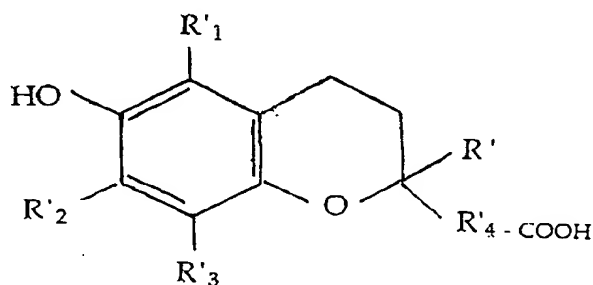
6. The chemical composition of claim 5 wherein the heme-protein macromolecule is a hemoglobin species.
7. A chemical composition according to claim 1 consisting essentially of the reaction product of an oxygen transporting compound and a 6-hydroxy chroman compound having antioxidant properties and corresponding to the general formula:



where each of R_1 , R_2 , and R_3 , is independently selected from H, $C_1 - C_8$ alkyl and $(CH_2)_n X$ where n is an integer from 0 to 20; each of R_1 , R_4 , R_5 and R_6 is independently selected from H, $C_1 - 20$ alkyl, X and $(CH_2)_m X$ where m is an integer from 0 - 20; and X is a substituent containing a reactive functional group selected in conjunction with the chosen oxygen transporting compound so as to be capable of reaction therewith to effect chemical linkage of the oxygen transporting compound to the chroman compound; with the proviso that the chroman compound includes at least one functional group X.

8. The chemical composition of claim 7 wherein the oxygen transporting macromolecule is a heme-protein macromolecule and the substituent X contains a functional group capable of reacting with amino acid residues of the protein chains of the heme protein macromolecule.

9. The composition of claim 8 wherein the heme-protein macromolecule is a hemoglobin species.
10. The composition of claim 8 or claim 9 wherein the substituent X contains a functional group selected from halo, carboxyl, amino, hydroxyl, thiol, azide, azo, aldehyde and phosphate.
11. The composition of any of claims 7 - 10 wherein the chroman compound is a chroman carboxylic acid corresponding to the general formula:



- where R' is H or an alkyl radical of 1-20 carbon atoms and R'1, R'2 and R'3 are independently selected from H and C1-C4, alkyl, and R1, is a direct bond or C1 - 8 alkyl chain.

12. The composition of claim 11 wherein the composition is a covalently linked conjugate of said chroman compound and human hemoglobin,
13. The composition of any of claims 6, 9, 10, 11 or 12 wherein the hemoglobin of the conjugate is modified by a cross-linking agent.
14. The composition of claim 13 wherein the hemoglobin is at least partially stabilized by said cross-linking agent to form stabilized tetrameric units.

15. The composition of any of claims 6 and 9 - 14 wherein the hemoglobin of the conjugate is at least partially oligomerized into oligomers of up to twelve stabilized tetrameric units.
- 5 16. The composition of any of claims 6 and 9 - 15 comprising a mixture of tetrameric stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant and oligomers of from 2 - 8 such stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant.
- 10 17. The composition of any of claims 13 - 16 wherein the hemoglobin is modified or cross-linked with a polyaldehyde, glutaraldehyde, a diaspirin compound, a pyridoxyl compound or a trimesoyl compound.
- 15 18. The composition of claim 17 wherein the hemoglobin is cross-linked with a polyaldehyde derived from oxidative ring-opening of a polysaccharide.
- 20 19. The composition of claim 18 wherein the polysaccharide is raffinose.
- 20 20. The composition of any of claims 6 and 13 - 19 wherein the hemoglobin-antioxidant conjugate is bonded to a biocompatible polymer.
21. The composition of claim 20 wherein the biocompatible polymer is polyethylene glycol, a polysaccharide, a polyamino acid, or an insoluble support.
- 25 22. The composition of claim 11 wherein, in the formula of the chroman carboxylic acid, at least one of R_1 , R_2 and R_3 is methyl.

23. The composition of claim 22 wherein, in the formula of the chroman carboxylic acid, R_4 is a direct bond.
24. The composition of any of claims 9 - 23, wherein the chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol.
25. A process of preparing a hemoglobin composition having antioxidant properties, which comprises chemically reacting hemoglobin and a hydroxy chroman compound as defined in claim 7 to form a covalently linked chemical conjugate thereof.
26. The process of claim 25 wherein, prior to conjugation to the chroman carboxylic acid, the hemoglobin is reacted with a cross-linking reagent.
27. The process of claim 25 wherein the hemoglobin-chroman carboxylic acid conjugate is subsequently reacted with a hemoglobin cross-linking reagent.
28. The process of claim 26 or claim 27 wherein the cross-linking reagent is a polyaldehyde.
29. The process of claim 28 wherein the polyaldehyde is o-raffinose.
30. The process of claim 29 wherein the hemoglobin is at least partially oligomerized by further reaction with o-raffinose
31. The process of any of claims 25 - 30 wherein the reaction between hemoglobin and the hydroxy chroman compound is conducted in the presence of an activating compound,

32. The process of claim 31 wherein the activating compound is a carbodiimide.
33. The process of claim 32 wherein the carbodiimide is 1(3-dimethylaminopropyl)-3-ethyl carbodiimide.
- 5 34. The process of any of claims 25 - 33 wherein the chroman carboxylic acid is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol.
- 10 35. Use, in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients, of a chemical composition as defined in any of claims 1 - 24.

0925157-010802